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ORIGINAL RESEARCH

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Vitamin B12 effectiveness in the management of hospitalized COVID-19 and its clinical outcomes and complications: A randomized clinical trial

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Abstract

Background and Aims: Since 2019, severe acute respiratory syndrome coronavirus 2, has spread and challenged the health care system for treatment which is mainly limited to supportive care. It is well-established that malnutrition impedes the immunity in human bodies, and makes it vulnerable to microorganisms. Vitamin B12 is one of the agents that has critical roles in body systems. Thus, the following clinical trial was conducted to assess its possible therapeutic value in COVID-19 patients.

Method: The present randomized clinical trial was carried out in Baharlou Hospital, and patients with confirmed COVID-19 infection within 24 h of admission were included. We used quadruple blocks randomization to divide patients into groups of case and control. The case group received 1000 mg of vitamin B12, daily for 7 day while the patients in control group were administered distilled water as placebo. The studied outcomes were duration of hospitalization, need for intensive care unit (ICU), mechanical ventilation, mortality rate and laboratory findings. The statistical analysis was done via SPSS version 22.

Results: After implementing inclusion and exclusion criteria, 34 participants were included in the study, 20 of which were male. Serum levels of creatinine, LDH (Lactate dehydrogenase), Ferritin, and CRP (C-reactive protein) had decreased in both groups. The improving changes of CRP, LDH, ferritin and creatinine was higher in case group. The increase of Alanine Transaminase and D-dimer was higher in control group. however there was no statistically significant difference. More patients were admitted to ICU in the control group but the difference was not statistically significant. Duration of hospitalization did not differ statistically between the groups. No in hospital mortality has been recorded.

Conclusion: Our study suggests that vitamin B12 supplementation seem to have curative effect in COVID-19. Nutritious diet is necessary for proper functioning of the immune system. Since malnutrition is associated with poor prognosis in COVID-19 patients, and limited number of participants in this study, we suggest performing meta-analysis on similar studies to reach reliable result.

KEYWORDS

B12, Covid, Covid-19, vitamin B12

1 | INTRODUCTION

The COVID-19 virus, which was reported for the first time in Wuhan, China in December 2019, is an acute respiratory infection that spread as a pandemic.[1] COVID-19 considerably increased the workload in health care system and put massive burden on economic system and society. With over 7 million cases and 144,672 deaths, Iran ranked 18th among the countries involved.[1,2] The clinical presentation of COVID-19 varies from asymptomatic infection to critical illness. Due to the fact that it is a multiorgan disease, kidney, liver and heart damages, as well as secondary infections have been expected.[1,3–5]

Since there is no specific treatment for COVID-19, addressing its modifiable aggravating factors can possibly lower the intensive care unit (ICU) admission rate, hospitalization duration, and mortality rate.[1] It is evident that poor nutritional status is associated with high mortality, and essential nutrients play an important role in the immunity system.[6–8] Moreover, gastrointestinal involvement specially in elderly patients suffering from COVID-19 can lead to severe nutritional deficiency and as a result the disease progression.[3,9] Among the essential nutrients, group B vitamins (e.g. B1, B2, B6, and B12), vitamin C, and vitamin D seem to reduce the duration of hospitalization.[7] The European Food Safety Authority (EFSA) has considered six vitamins-A, B6, B12, C, D, Folate- and four minerals-zinc, copper, iron and selenium- essential for normal function of the immune system.[10,11]

Vitamin B12 participates in the oxygenation of red blood cells, immune system response, antibody production, microbiome of digestive tract, coagulation pathways, and inflammatory response. Accordingly, providing sufficient amounts of vitamin B12 can be effective in the course of the disease.[12–15] Also, the therapeutic role of vitamin B12 in sepsis and SIRS has already been proven.[16] Research on the spread of COVID-19 pandemic in European countries showed that the countries with highest intake of vitamin B12, such as Finland and Portugal, are less affected by the pandemic. Whereas, countries with vitamin B12 intake lower than the median (negative z score), such as Belgium and Spain, had the highest rate of involvement.[11] Thus, it is plausible to suppose that the vitamin B12 supplementation and nutritional status can lower the incidence rate in COVID-19.[14]

Studies on the correlation between nutritional factors and the prognosis of COVID-19 can help governments and health care systems in terms of prevention and treatment.[8] Hitherto, there is no existent specific protocol incorporating vitamin B12 in COVID-19 treatment.[15] Considering the importance of the COVID-19 pandemic, and the probable effect of malnutrition on its outcome, this study was designed to investigate the possible therapeutic effects of vitamin B12 in COVID-19 patients, and help with treatment protocols.

Key Points

- Some nutritional elements like vitamin B12 are involved in human body's immune system.
- Vitamin B12 supplementation is capable of lowering inflammatory laboratory values such as C-reactive protein, lactate dehydrogenase.
- Malnutrition is a prognostic factor for the covid-19 outcome.

2 | METHODS

2.1 | Study design

This study was conducted on adults with COVID-19 admitted to Baharlou Hospital, one of the main educational and referral hospitals of Tehran University of medical science, Tehran, Iran, from October 2021 till February 2022. Patients between 18 and 75 years of age were included in the study, and they had to have positive COVID-19 PCR test within the first 24 h of hospitalization. Patients younger than 18, patients with chronic kidney disease, liver failure, patients requiring mechanical ventilation and NIV masks, were excluded from the study. We used block randomization and quadruple blocks to divide the patients into case and control groups. Vitamin B12 1000 mg/daily was administered orally to the case group for 7 days,[17] and identical vials of distilled water were given to the control group as placebo. The treatment must have been completed under observation, therefore any patient discharged before the 6 days, was excluded from the study. This study is approved by Research Ethics Committee of Tehran University of Medical Sciences and is registered under IR.TUMS.MEDICINE.REC.1400.729. A written informed consent was obtained from each patient.

We recorded the data regarding patients' characteristics including age, sex, admission and discharge date. All the included patients were visited at the day of admission and laboratory values of vitamin B12 and other parameters including Cr, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-Dimer, Alanine Transaminase (ALT) were determined before intervention. We ordered the aforementioned laboratory values at the end of invention for each patient. Moreover, we measured the mean hospitalization stay, frequency of ICU admission, need for mechanical ventilation, and mortality rate in each group. The laboratory values were reported quantitatively and we calculated the mean with standard deviation, and compared them between the two groups at inception. In addition, the change for each parameter was calculated and its significancy was determined in the groups, and then was compared between the groups.

For numerical variables, we determined their normality first, and used parametric and non-parametric tests accordingly *T-test* in two groups and one-way analysis of variance in three groups will be used to compare the means for quantitative variables. *Chi-square test* is also used to compare qualitative variables. We also used Logistic regression to examine the relationship between vitamin B12 consumption and the evaluated outcomes, such as death due to the disease or the severity of the disease (admission to the ICU). We reported the results with a confidence interval of 95% and a p Value of less than 0.05 was considered significant. All the analysis in this study was performed via SPSS version 22.

3 | RESULTS

After implementing the exclusion criteria, 34 patients with confirmed COVID-19 were left, including 20 men and 14 women. For case and control groups, the median age was 52.6, and 49.92 (p Value: 0.681), the duration of hospitalization was 7.47 and 7.41 (p Value: 0.966), and the mean level of vitamin B12 was 530.92 and 896.36 (p Value: 0.149), respectively. Patients' characteristics parameter can be seen in Table 1. All the parameters that we assessed and analyzed are shown in Table 2.

We checked the parameters at admission, during, and on the last day of hospitalization and analyzed the differences between the groups and their changes. We found that on the first day of hospitalization, the CRP level was significantly higher in the case group (p Value: 0.045). On the last day of hospitalization, the WBC count was significantly higher in the case group. As shown in Table 3, the CRP, LDH, and creatinine levels had significant improving changes in the case group, while the changes in CRP, LDH, and ALT levels in the control group were significant. We observed higher improving changes in other parameters like ferritin, ALT in the case group, indicating a good response to therapy; however, there were no significant differences between the changes.

ICU admission rate was higher in the control group, but no statistical significance was observed. (p Value: 0.688).

4 | DISCUSSION

The COVID-19 pandemic arose in 2019 and has been continuing to these days, and is caused by a respiratory virus, severe acute respiratory syndrome coronavirus 2, with multiorgan involvement and inflammation.[18] The aim of this study was to benefit the treatment protocol of COVID-19 through the possible effectiveness of vitamin B12. In general, malnutrition is implicated in the disease progression and is associated with poor outcome.[19] Among nutrients, vitamin B12 is essential for the proper functioning of the immune

TABLE 1 Patients characteristic.

Duration (day)	Mean	SD
Int.	7.47	2.93
Cont.	7.41	4.88
p Value: 0.966		
Vit B12	Mean	SD
Int.	530.92	459.84
Cont.	896.36	757.06
normal range: 110-800 pg/mL		
p Value: 0.149		
Age	Mean	SD
Int.	52.6	17.3
Cont.	49.92	17.32
p Value: 0.681		
ICU admission	Mean	Percent
Int.	1	5.8
Cont.	4	23.5
p Value: 0.146		

TABLE 2 Variables before and after and p Value.

Ferritin		Mean	SD	p Value
Before	Int.	427.31	308.76	0.47
	Cont.	352.58	284.68	
After	Int.	381.21	219.83	0.68
	Cont.	346.14	247.93	
WBC		Mean	SD	p Value
Before	Int.	7.27	4.11	0.87
	Cont.	7.48	2.99	
After	Int.	10.05	2.90	0.04
	Cont.	8.22	2.17	
ALT		Mean	SD	p Value
Before	Int.	56.88	50.12	0.06
	Cont.	30.47	26.33	
After	Int.	64.52	36.84	0.13
	Cont.	45.58	33.49	
Cr		Mean	SD	p Value
Before	Int.	1.02	0.18	0.75
	Cont.	1.05	0.32	
After	Int.	0.90	0.13	0.16
	Cont.	0.98	0.19	
CRP		Mean	SD	p Value
Before	Int.	78.15	44.35	0.04
	Cont.	49.81	34.09	
After	Int.	36.73	39.69	0.26
	Cont.	23.28	27.67	
LDH		Mean	SD	p Value
Before	Int.	796.82	285.97	0.22
	Cont.	673.56	285.31	
After	Int.	449.82	214.22	0.2
	Cont.	372.37	101.04	
D-dimer		Mean	SD	p Value
Before	Int.	1.52	0.51	0.37
	Cont.	1.68	0.47	
After	Int.	1.58	0.50	0.1
	Cont.	1.85	0.36	

Abbreviations: ALT, Alanine Transaminase; Cr, creatinine; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, White Blood Cells.

TABLE 3 Variables and change.

Ferritin		Change	SD	*p* (in)	*p* (among)
Groups	Int.	−46.10	255.58	0.48	0.83
	Cont.	−29.78	147.81	0.45	
WBC		Change	SD	*p* (in)	*p* (among)
Groups	Int.	2.78	3.70	0.01	0.07
	Cont.	0.74	2.69	0.27	
Alt		Change	SD	*p* (in)	*p* (among)
Groups	Int.	7.64	27.30	0.26	0.33
	Cont.	15.11	14.76	<0.001	
Cr		Change	SD	*p* (in)	*p* (among)
Groups	Int.	−0.12	0.14	0.002	0.49
	Cont.	−0.07	0.27	0.27	
CRP		Change	SD	*p* (in)	*p* (among)
Groups	Int.	−41.41	50.28	0.004	0.35
	Cont.	−26.52	40.25	0.01	
LDH		Change	SD	*p* (in)	*p* (among)
Groups	Int.	−347	283.36	<0.001	0.87
	Cont.	−330.26	284.50	<0.001	
D-dimer		Change	SD	*p* (in)	*p* (among)
Groups	Int.	0.05	0.55	0.67	0.4
	Cont.	0.24	0.42	0.08	

system and its deficiency can potentially worsen the disease course in COVID-19. There are multiple studies that have shown vitamin B12 deficiency is a prevalent phenomenon. Azar cohort study, reported vitamin B12 deficiency in 77% of men and 51% of women, and according Shams study, 27% of population in Iran have vitamin B12 deficiency.[16,20]

There is limited data regarding vitamin B12 efficacy in COVID-19 treatment, and its therapeutic role in this disease is a matter of debate.[21] Due to this controversy, and for the development of new treatment protocols for COVID-19 treatment, the present study was conducted.[8] Several studies have assessed the effect of malnutrition in COVID-19 prognosis.[22,23] In a study designed by TAN et al. in which the DMB (vitamin D, magnesium, vitamin B12) treatment was given to patients, a positive effect was observed.[24] It should be also noted that malnutrition in COVID-19 patients should be addressed as early as the day of hospitalization and even after discharge.[25,26]

In our study, the number of people hospitalized in the ICU was higher in the control group compared to the case group, 5% and 23% respectively. This finding is in accordance with other studies in which a positive correlation between vitamin B12 deficiency and ICU mortality has been shown.[15] In Shakeri et al.'s study, the ICU admission and mortality rates were 12% and 14%, respectively, and the serum level of vitamin B12 was lower in ICU cases compared to non-ICU cases, although the difference was not significant. This study proposed that people with higher level of vitamin B12 are less likely to need ICU, and less prone to death, but the difference was not significant.[13] The same pattern was observed in our study, that the need for ICU in the control group was four times more than cases, though not statistically significant. This can be due to the limited number of participants and the fact that our study was carried out in a referral center. No in hospital mortality has been recorded.

Another study shows that unlike vitamin B5, B6, B7 that need high intake to affect the outcomes of COVID-19, only moderate intake of vitamin B12 can have a protective effect against COVID-19.[27] In a study by Corcoran and colleagues, data of 129 patients were analyzed and as a result, Vitamin B12 level was positively correlated with CRP level and CRP was significantly higher in survivors. Same study showed Vitamin B12 level was significantly higher in nonsurvivor. They suggested that this finding might be due to the lack of appropriate reference ranges and confounders.[28] In a study, 36 health care workers with a history of COVID-19 were evaluated and the results indicated that IgM level is positively correlated with vitamin B12 level.[29]

The contrast between the aforementioned studies and ours is that none of the participants in our study had malnutrition, in addition they did not have vitamin B12 deficiency except for one. This highlights the need for structured studies with coherent study groups to examine the full extent of Vitamin B12 role in COVID-19. The sample of this study was limited due to the requirement of 7 days hospitalization. To ensure that all patients have received full treatment patients whose treatment were not completed under observation in the hospital were excluded from the study. Retrospectively, this limits the number of patients while maintaining the structure and reliability of method. Therefore, performing meta-analysis on these data will be of interest to researchers.

5 | CONCLUSION

All in all, our study showed that vitamin B12 supplementation seem to be effective in the management of COVID-19, and have an effect on improving the inflammatory factors and the overall outcome will improve. moreover, a nutritious diet is proven to be essential for proper system functioning, thus malnutrition can potentially lead to disease burden. Some studies have suggested that Vitamin B12 enhances the immune system functionality, reduces gastrointestinal complications, and ameliorates breathing difficulties. Due to these findings, for establishing the role of malnutrition in COVID-19, we need more research about vitamin B12 and COVID-19.

AUTHOR CONTRIBUTIONS

Zahra Erfani: Conceptualization; data curation; investigation; writing—original draft; writing—review and editing. **Nafiseh Alizadeh**: Conceptualization; methodology; project administration; supervision; validation. **Neda Faraji**: Conceptualization; data curation; project administration; supervision. **Alireza Teymouri**: Formal analysis; methodology; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

the data regarding this paper is available through the corresponding author reasonable request.

ETHICS STATEMENT

This study is approved by Research Ethics Committee of Tehran University of Medical Sciences and is registered under IR.TUMS.MEDICINE.REC.1400.729. All participants signed informed written consent.

TRANSPARENCY STATEMENT

The lead author Nafiseh Alizadeh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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